Case Report

Primary Intracranial Squamous Cell Carcinoma: Case Report and Literature Review

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Abstract

Intracranial Squamous Cell Carcinoma (SCC) is a rare condition and relatively few cases have been described in the literature. Despite the poor prognosis, no standardized treatment protocols have been developed. In this article, we report a case of primary intracranial SCC with a review of the literature. A 42-year-old woman presented with intracranial SCC in the right cerebellopontine angle. The patient underwent gross total resection of the tumour followed by adjuvant radiotherapy (50 Gy in 25 fractions). The patient died 26 months after the initial treatment due to leptomeningeal progression without local relapse. This case illustrates the complexity of this rare condition and the need for multimodal management.

Keywords: Epidermoid cyst; Squamous cell carcinoma; Primary; Intracranial; Malignant transformation.

Introduction

Intracranial epidermoid cysts are rare but generally benign intracranial tumours [1,2]. These cysts can undergo malignant transformation into squamous cell carcinoma (SCC), but only a few such cases have been described since the first report in 1912 [1]. Intracranial SCC may originate from a known intracranial epidermoid cyst or it may be a de novo tumour [3].

Here we report a case of primary intracranial SCC. In addition, we review the literature on this rare tumour type.

Case report

History and examination

A 42-year-old woman presented with a 6-month history of right-side deafness and a 5-month history of dizziness and tinnitus. She had no relevant medical history.

Imaging studies

Contrast-enhanced Computed Tomography (CT) revealed a lesion with multicystic heterogeneous enhancement and Magnetic Resonance Imaging (MRI) showed a right Cerebellopontine Angle (CPA) mass invading the right inner auditory canal (Figure 1).
These radiological features, together with the clinical presentation, mimicked a schwannoma of cranial nerve VIII.

**Surgical treatment and postoperative course**

A right retrosigmoid craniotomy with gross total resection of the tumour was performed on November 13, 2019. Intraoperatively, the macroscopic appearance of the tumour was heterogeneous, consisting of fibrous, highly vascularized areas alternating with necrotic and cystic areas. The tumour was indistinguishable from an acoustic schwannoma. The postoperative course was uneventful and the patient was discharged home with no new neurological deficits. During clinical follow-up, the dizziness decreased and the tinnitus resolved, but the ipsilateral hypoacusis remained unchanged.

**Pathological findings**

Histologic examination of the resected specimen revealed a solid-cystic lesion lined by squamous epithelium with moderate atypia and abundant mitotic figures consistent with SCC (Figure 2). These features were suggestive of a primary central nervous system SCC arising from a pre-existing epidermoid cyst.

To rule out the presence of an extracranial primary tumour, Positron Emission Tomography (PET) was performed. The results of this scan were normal.

**Radiation therapy**

This case was presented to a multidisciplinary tumour board, which decided that the patient was a candidate for adjuvant radiotherapy. Fractionated stereotactic radiotherapy was prescribed (50 Gy in 25 fractions) (Figure 3). The treatment was well-tolerated and the final session was delivered in late February 2020.

**Treatment outcomes**

An MRI performed in June 2020 (7 months after surgery) revealed focal enhancement in the surgical margin on the right cerebellar peduncle and a thin enhancement in the right internal acoustic canal. On a follow-up MRI (January 2022), the previous findings remained stable, but revealed the presence of leptomeningeal progression in the cervical and thoracic spinal cord, resulting in spinal cord compression (Figure 4a,b). Consequently, local radiotherapy (30 Gy in 10 fractions) was administered to that region. The patient started intrathecal treatment with methotrexate in March 2022. A follow-up MRI (April 2022) revealed leptomeningeal progression with secondary spinal cord compression from T9 to T11. Another course of radiotherapy was prescribed (30 Gy). However, the patient did not complete radiotherapy (receiving only 6 Gy) (Figure 5a,b) and died on May 5, 2022 due to neurological impairment.

**Methods and results**

We performed a systematic review of the literature using the criteria established in the Preferred Reporting Items for Systematic Review and Meta-analyses (PRISMA). We searched the PubMed and Medline databases for relevant articles published through March 31, 2021 using the following search terms were used: “intracranial squamous cell carcinoma” OR “intracranial epidermoid cyst” OR “malignant transformation of intracranial epidermoid cyst”. The inclusion and exclusion criteria are shown in Figure 6.

A total of 90 articles were identified for further review. Of these, 69 case reports describing secondary malignant transformation of intracranial epidermoid cysts were identified (Table 1). Most of the patients described in these case reports were males (n=41; 59.4%). The mean age was 52.5 years (range, 20-77). Six of the cases were diagnosed during the autopsy.

In most cases (61/69; 88.4%) surgery was the primary treatment. Thirty-one patients received adjuvant radiotherapy (conventional radiotherapy, radiosurgery, or proton beam therapy), with or without chemotherapy.

Apart from the current case, a total of ten cases involving primary intracranial SCC have been reported to date (Table 2). The most commonly reported location is the CPA (5/10 cases), which was the same area as secondary malignant carcinomas. Most of these patients (8/10) underwent surgery, with four also receiving adjuvant radiation therapy. Of the two nonsurgical patients, one received definitive radiotherapy and the other was diagnosed at autopsy.
Figure 3: Radiation therapy treatment planning and dose distribution. (a) The image on the left shows the contouring of the proposed treatment. The tumour bed is contoured in blue and the original mass in light green. (b) The image on the right shows the dose distribution with 95% isodose curves (47.5 Gy).

Figure 4: First evidence of progression on T1-weighted MRI on January 2022.

Figure 5: T1-weighted MRI (April 2022) showing the second and final evidence of progression in the cervicothoracic (a) and thoracolumbar (b) regions.

Figure 6: Prisma flow diagram.

Discussion

Intracranial epidermoid cysts account for 0.2-1.8% of all intracranial tumours [2,3]. These tumours are generally slow growing and histologically benign. Malignant transformation of an epidermoid tumour is rare and de novo intracranial SCC is even more uncommon.

The first case of SCC was reported by P. Ernst in 1912. This case involved a 52-year-old man diagnosed with SCC of the CPA arising from a known epidermoid cyst [1]. Since that time, a total of 73 cases of malignant transformation of epidermoid cysts have been reported [2,4]. Primary intracranial SCC was first described in 1976 by Wong et al. [5]. To our knowledge, only nine other cases have been reported since [6-14].

Intracranial SCC appears to be more common in males [6,15,16], although Lakhdar et al described a greater predominance in women [9].

Hamlat et al. [16] classified SCC into five different categories according to the type of malignant transformation, as follows: 1) initial malignant transformation of an epidermoid cyst, which is the most common type; 2) malignant transformation from a remnant epidermoid cyst; 3) malignant transformation with leptomeningeal carcinomatosis (LC); 4) SCC carcinoma arising from other benign cysts; and 5) other malignancies arising in benign cysts.

Malignant transformation

Based on the available reports, malignant transformation can occur anywhere from 3 months to 33 years from diagnosis of the benign lesion [16], with a median interval of 24 months [15].

Diagnosis

The symptoms of SCC are non-specific, which is why diagnosis can be challenging. Selection of the appropriate diagnostic tests depends on the symptoms, which vary according to the tumour location. Rapid progression of symptoms may be an important clinical sign of malignant transformation [6].
Table 1: Reported cases of malignant transformation from epidermoid tumours.

<table>
<thead>
<tr>
<th>Author and year</th>
<th>Age (Sex)</th>
<th>Location</th>
<th>Treatment</th>
<th>Dose</th>
<th>Survival status at last evaluation (time from surgery)</th>
<th>Interval to MT, months</th>
</tr>
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<tbody>
<tr>
<td>Ernst 1912 [1]</td>
<td>52(M)</td>
<td>CPA</td>
<td>Autopsy</td>
<td>NS</td>
<td>Deceased (8 months)</td>
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</tr>
<tr>
<td>Hug 1942 [27]</td>
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<td>Parapontine</td>
<td>Autopsy</td>
<td>NS</td>
<td></td>
<td></td>
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<td>Yamanaka 1955 [28]</td>
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<td>Base of brain</td>
<td>Autopsy</td>
<td>NS</td>
<td></td>
<td></td>
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<tr>
<td>Davidson 1960 [29]</td>
<td>46(M)</td>
<td>Frontal</td>
<td>S + RT</td>
<td>50 Gy</td>
<td>Deceased (2 months)</td>
<td>NS</td>
</tr>
<tr>
<td>Landers 1960 [30]</td>
<td>73(F)</td>
<td>Cerebellar</td>
<td>Autopsy</td>
<td>NS</td>
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<td>Komjatseg 1964 [31]</td>
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<td>12</td>
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<td>Fox 1965 [33]</td>
<td>43(M)</td>
<td>Temporal lobe</td>
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<td>84</td>
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<td>Dubois 1981 [34]</td>
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<td>Fourth ventricle</td>
<td>S + RT</td>
<td>50 Gy</td>
<td>Deceased (2 months)</td>
<td>NS</td>
</tr>
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<td>53(F)</td>
<td>CPA</td>
<td>Autopsy</td>
<td>NS</td>
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<td>Lewis 1983 [36]</td>
<td>54(F)</td>
<td>Parasellar</td>
<td>S</td>
<td>Deceased (1 month)</td>
<td>36</td>
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<td>45(M)</td>
<td>Parieto-Occipital</td>
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<td>NS</td>
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<tr>
<td>Goldman 1987 [40]</td>
<td>59(F)</td>
<td>Intraventricular</td>
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<td>Alive (36 months)</td>
<td>396</td>
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<td>Salazar 1987 [41]</td>
<td>49(M)</td>
<td>CPA + pons</td>
<td>S + RT</td>
<td>NS</td>
<td>Alive (10 months)</td>
<td>3</td>
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<td>Abramson 1989 [42]</td>
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<td>CPA</td>
<td>S</td>
<td>Deceased (1 month)</td>
<td>24</td>
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<tr>
<td>Nishiura 1989 [43]</td>
<td>38(M)</td>
<td>CAP</td>
<td>S + ChT</td>
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<td>6</td>
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<td>39(M)</td>
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<td>50 Gy</td>
<td>Deceased (15 months)</td>
<td>6</td>
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<td>Deceased (1 month)</td>
<td>372</td>
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<tr>
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<td>62(M)</td>
<td>Parasellar</td>
<td>S</td>
<td>Deceased (1 week)</td>
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<td>Nishio 1995 [47]</td>
<td>57(M)</td>
<td>CPA</td>
<td>S + RT</td>
<td>50 Gy</td>
<td>Alive (30 months)</td>
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<td>Nishio 1995 [47]</td>
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<td>Middle-posterior fossa</td>
<td>S + RT</td>
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<td>Deceased (3.5 months)</td>
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<tr>
<td>Uchino 1995 [48]</td>
<td>57(M)</td>
<td>CPA</td>
<td>S + RT</td>
<td>60 Gy</td>
<td>Alive (4 months)</td>
<td>18</td>
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<tr>
<td>Ogata 1996 [49]</td>
<td>63(F)</td>
<td>Dorsolateral pons</td>
<td>S</td>
<td>Recurrence (3 months)</td>
<td>NS</td>
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<td>Mohanty 1996 [50]</td>
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<td>Posterior fossa</td>
<td>S + RT</td>
<td>NS</td>
<td>Deceased (11 months)</td>
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<td>Lateral ventricle</td>
<td>S</td>
<td>Deceased (1 month)</td>
<td>372</td>
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<td>Murase 1999 [52]</td>
<td>50(F)</td>
<td>CPA</td>
<td>S + ChT + SRS</td>
<td>14 Gy</td>
<td>Alive (60 months)</td>
<td>120</td>
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<tr>
<td>Asahi 2001 [53]</td>
<td>55(F)</td>
<td>CPA</td>
<td>S</td>
<td>Deceased (3 months)</td>
<td>66</td>
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<td>Nawashiro 2001 [24]</td>
<td>46(M)</td>
<td>Left temporal lobe</td>
<td>S</td>
<td>NS</td>
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<td>NS</td>
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<tr>
<td>Khan 2001 [54]</td>
<td>53(M)</td>
<td>Prepontine</td>
<td>BSC</td>
<td>Deceased (10 months)</td>
<td>7</td>
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<td>Link 2002 [55]</td>
<td>57(F)</td>
<td>CPA</td>
<td>S + RT + SRS</td>
<td>45 Gy + 15 Gy</td>
<td>Deceased (32 months)</td>
<td>12</td>
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<td>Monaco 2003 [56]</td>
<td>36(M)</td>
<td>Cisterna magna</td>
<td>S</td>
<td>Alive (24 months)</td>
<td>6</td>
<td></td>
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<tr>
<td>Shirabe 2003 [57]</td>
<td>49(M)</td>
<td>Ventral pons</td>
<td>S + RT</td>
<td>60 Gy</td>
<td>Deceased (42 months)</td>
<td>18</td>
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<td>54(F)</td>
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<td>ChT</td>
<td>Deceased (7 months)</td>
<td>3</td>
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<td>Park 2003 [59]</td>
<td>65(F)</td>
<td>CPA</td>
<td>S + RT</td>
<td>50 Gy</td>
<td>Alive (6 months)</td>
<td>NS</td>
</tr>
<tr>
<td>Michael 2005 [60]</td>
<td>45(M)</td>
<td>Petroclival</td>
<td>S + RT + ChT</td>
<td>59.4 Gy</td>
<td>Deceased (12 months)</td>
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<td>Tamura 2006 [22]</td>
<td>56(F)</td>
<td>CPA</td>
<td>S + SRS</td>
<td>15 Gy</td>
<td>Alive (13 months)</td>
<td>96</td>
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<tr>
<td>Kodama 2007 [61]</td>
<td>67(M)</td>
<td>CPA</td>
<td>S + SRS</td>
<td>14 Gy</td>
<td>Deceased (11 months)</td>
<td>NS</td>
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<td>Pagni 2007 [62]</td>
<td>65(F)</td>
<td>Pineal</td>
<td>S</td>
<td>NS</td>
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<td>NS</td>
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<td>Agarwal 2007 [63]</td>
<td>45(M)</td>
<td>Posterior fossa</td>
<td>S</td>
<td>NS</td>
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<td>Author, year</td>
<td>Age (sex)</td>
<td>Location</td>
<td>Treatment</td>
<td>Dose</td>
<td>Survival status at last evaluation (time from surgery)</td>
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<td>Wong 1976 [5]</td>
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<td>Parapontine</td>
<td>Autopsy</td>
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<td>Deceased (1 day)</td>
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<td>Nosaka 1979[7]</td>
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<td>CPA</td>
<td>S</td>
<td></td>
<td>Deceased (7 months)</td>
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<tr>
<td>Garcia 1981 [18]</td>
<td>61(M)</td>
<td>CPA</td>
<td>RT</td>
<td>NS</td>
<td>Deceased (9 months)</td>
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<tr>
<td>Ebisudani 1990 [8]</td>
<td>68(M)</td>
<td>CPA</td>
<td>S</td>
<td></td>
<td>Deceased (1 month)</td>
<td></td>
</tr>
<tr>
<td>Jain 2003 [9]</td>
<td>5(F)</td>
<td>Temporal lobe</td>
<td>S + ChT + RT</td>
<td>NS</td>
<td>Alive (10 months)</td>
<td></td>
</tr>
<tr>
<td>Mallick 2012 [10]</td>
<td>35(F)</td>
<td>Frontal lobe</td>
<td>S + RT</td>
<td>60 Gy</td>
<td>Alive (12 months)</td>
<td></td>
</tr>
<tr>
<td>Liu 2018 [12]</td>
<td>20(M)</td>
<td>Sellar</td>
<td>S</td>
<td></td>
<td>Alive (9 months)</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** MT: Malignant Transformation; M: Male; F: Female; CPA: Cerebellopontine Angle; S: Surgery; RT: Radiation Therapy; SRS: Stereotactic Radiosurgery; PB: Proton Beam; ChT: Chemotherapy; BSC: Best Supportive Care; NS: Not Specified.

**Table 2:** Reported cases of primary intracranial squamous cell carcinoma.
Primary intracranial squamous cell carcinomas are rare and the optimal treatment approach remains unclear. The most common approach appears to be surgery with adjuvant radiotherapy. Nevertheless, the probability of long-term survival in these patients remains low, even in those who undergo gross total resection with adjuvant radiotherapy.

In the present case, the presence of leptomeningeal progression (Figures 4 and 5) underscores the importance of neural axis irradiation of the entire neuroaxis should be considered as this treatment could potentially improve survival outcomes.

**Abbreviations:** M: male; F: female; CPA: cerebellopontine angle; S: surgery; RT: radiation therapy; SRS: stereotactic radiosurgery; ChT: chemotherapy; NS: not specified.

**Diagnostic criteria**

In 1982, Garcia et al. [18] proposed the following diagnostic criteria for primary intracranial SCC: Tumour limited to the intracranial, intradural compartment without extension beyond the dura, cranial orifices, or connection with the middle ear, air sinuses, or sella turcica. Nasopharyngeal cancer must also be ruled out. According to those authors, only cases that meet all of these criteria should be considered primary intracranial SCC. In their study, Hamlat and colleagues [16] included two other diagnostic criteria: the presence of a benign squamous cell epithelium within the malignant tumour and the absence of metastatic carcinoma.

**Radiological findings**

The most commonly reported location of these lesions is the CPA (45% of cases), followed by the temporal lobe (12%), and, less commonly, the preoptic area and cerebellum [15,17].

Most lesions described to date have a low signal intensity on T1-Weighted MRI Images (T1-WI) and high signal intensity on T2-weighted images (T2WI) [4,20-22]. The presence of contrast enhancement and oedema may be key findings suggestive of malignant transformation [23]. Nawashiro et al. [24] found that epidermoid cysts could be differentiated from malignant tumours on Diffusion-Weighted Imaging (DWI), with a high signal on DWI in benign cysts versus a low signal in malignant transformations.

Leptomeningeal carcinomatosis, which is associated with a poor prognosis, has been reported in 27.8% of patients [4]. The development of LC may be due to leptomeningeal seeding by tumour cells or wide dissemination of malignant cells from an intradural primary lesion. Given that leptomeningeal metastases have been described in locations far from the primary lesion and without clear continuity, some authors have suggested that LC could also be due to surgical dissemination [25].

**Treatment**

In benign intracranial epidermoid lesions, the initial approach is usually surgery. By contrast, no standard approach has yet been developed for SCC. Liu et al. [4] categorized the treatment options into several groups, as follows: surgical management alone; surgery plus radiotherapy (either radiosurgery or stereotactic radiosurgery); chemotherapy alone; or chemotherapy in combination with either surgery or radiotherapy; or surgery plus one or more adjuvant therapies.

**Surgery**

Surgically-treated patients appear to have a significantly better prognosis than patients who receive palliative treatments (median survival: 25 vs. 8 months); moreover, gross total resection is associated with better survival outcomes than subtotal resections (median survival: 48 vs. 35 months, respectively) [15]. The addition of adjuvant radiotherapy to primary surgery is also associated with better survival than surgery alone (35 vs. 5 months, respectively) [15,17].

**Radiation therapy**

In the patients included in the studies in this review (Table 1), the mean radiation dose was 52.0 Gy (range, 36.0-67.2 Gy); however, higher doses were not associated with better survival outcomes [15,17]. Moreover, according to Alvord’s model [26], a 2 cm epidermoid tumour has a 90% probability of growth inhibition when the total dose is 50 Gy (2 Gy daily fractions), without an increased risk of radionecrosis or optic or neurocognitive impairment.

Tamura et al. [22] found that the addition of either conventional radiotherapy or radiosurgery to primary surgery positively impacted survival outcomes. In that study, median survival times for patients treated with surgery alone, surgery plus conventional radiotherapy, and surgery plus radiosurgery were 1,18, and 44 months, respectively.

**Chemotherapy**

Adjuvant chemotherapy may improve local control but its impact on survival is not clear due to the heterogeneous treatment protocols applied to date and to the limited number of reported cases in the literature.

**Survival**

Regardless of the specific treatment protocol, the reported recurrence rate is approximately 20%, with an average recurrence time of 17 months [15,16]. Median survival following detection of a recurrence is five months [15].

In patients with intracranial SCC, survival outcomes are poor, and most patients die within 12 months following symptom onset or diagnosis [16].

**Conclusion**

Primary intracranial squamous cell carcinomas are rare and the optimal treatment approach remains unclear. The most common approach appears to be surgery with adjuvant radiotherapy. Nevertheless, the probability of long-term survival in these patients remains low, even in those who undergo gross total resection with adjuvant radiotherapy.

In the present case, the presence of leptomeningeal progression (Figures 4 and 5) underscores the importance of neural axis follow-up. Moreover, given that leptomeningeal dissemination has been reported in close to 30% of patients, prophylactic irradiation of the entire neuroaxis should be considered as this treatment could potentially improve survival outcomes.
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